ITFG / IPAC Collaboration

BA / BE Technical Team

Review of In Vivo and In Vitro Tests in FDA's Draft Guidance on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action and Anticipated Forthcoming Guidance for Orally Inhaled Drugs

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I. EXECUTIVE SUMMARY

The International Pharmaceutical Aerosol Consortium (IPAC) and the Inhalation Technology Focus Group (ITFG) of the American Association of Pharmaceutical Scientists share the FDA's goal of assuring the highest levels of safety, efficacy and quality of orally inhaled and nasal drug products. The ITFG/IPAC Collaboration has identified several areas in the draft Guidance for Industry: *Bioavailability (BA) and Bioequivalence (BE) Studies for Nasal Aerosols and Nasal Sprays for Local Action*[1] where scientific rationale can be questioned and where more scientific discussion and debate are needed.

The ITFG/IPAC Collaboration encourages the Agency to solicit additional scientific discussion on BA/BE studies before issuing further guidance in this area. To resolve the outstanding issues expeditiously, the ITFG/IPAC Collaboration strongly recommends that the Agency pursue existing avenues for scientific collaboration between the Agency and outside interested parties, such as the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), or another AAPS/FDA/USP workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery.

[1] Draft Guidance for Industry *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* available at http://www.fda.gov/cder/guidance/index.htm (1999).

II. BACKGROUND

- Between October 1998 and June 1999, the FDA issued the following draft Guidances for Industry: 1) *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation*; 2) *Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation;* and 3) *Bioavailability (BA) and Bioequivalence (BE) Studies for Nasal Aerosols and Nasal Sprays for Local Action.*
- On 3-4 June 1999, the FDA/AAPS/USP sponsored a Workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery. At the Workshop, the International Pharmaceutical Aerosol Consortium (IPAC) proposed the creation of a post-Workshop consensus building process to address several issues in the draft Guidances for Orally Inhaled and Nasal Drug Products (OINDP).
- In October 1999,The Inhalation Technology Focus Group (ITFG) supported IPAC's proposal at the June Workshop and agreed to collaborate with IPAC in order to combine scientific expertise and regulatory knowledge and address key issues in the draft OINDP Guidance documents. The ITFG/IPAC Collaboration consists of five Technical Teams overseen by a Steering Committee. Over one hundred individuals from more than twenty companies are participating in the ITFG/IPAC Collaboration. The BA/BE Team is formed to address BA/BE issues of OINDP.
- In October 1999, the FDA created the OINDP Expert Panel (currently the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science) to facilitate information sharing on scientific, technical, compendial and research issues relevant to the draft OINDP Guidances. On 26 April 2000, the OINDP Subcommittee held its first meeting, during which the ITFG/IPAC Collaboration reported on its work and made certain commitments to provide the Agency and OINDP Subcommittee with relevant technical reports.
- At the 26 April 2000 OINDP Subcommittee meeting, the BA/BE Technical Team of the ITFG/IPAC Collaboration reported that it has developed position statements on in vitro and in vivo testing in the FDA's draft BA/BE Guidance.
- The BA/BE Team's position statement on in vitro testing is: *In vitro testing is essential for pharmaceutical product equivalence and should be included as part of BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for BE approval without establishing in vivo BE.*
- The BA/BE Team's position statement on in vivo testing is: *For BE approval, BA/BE Guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for in vivo testing for local and systemic exposure, efficacy and safety.*
- At the 26 April meeting, the BA/BE Team committed to submit to the Agency and the OINDP Subcommittee a technical paper on the Team's in vitro and in vivo position statements. This is the topic of the present report.
- The Team also committed to providing the Agency and the OINDP Subcommittee with its perspectives on the BA/BE questions presented by the Agency during the OINDP Subcommittee meeting. A companion paper addressing these questions is being submitted to the Agency simultaneously with this technical report.

III. INTRODUCTION

The BA/BE Technical Team of the ITFG/IPAC Collaboration has focused on the in vitro and in vivo tests in the Agency's draft *Guidance for Industry Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (draft BA/BE Guidance). Since January 2000, the BA/BE Technical Team has discussed these issues in depth. The Team has agreed on several working assumptions and has identified two main position statements, one for in vitro tests and the other for in vivo tests in the draft BA/BE Guidance. During the past several months, Team members have submitted and evaluated data and scientific articles related to these position statements. The conclusions in this paper are based upon the Team's working assumptions and currently available information.

This paper is closely related to the paper which is being co-submitted by the BA/BE Team to respond to the BA/BE questions presented by the Agency at the OINDP Subcommittee meeting on 26 April. The paper presented here is more general in scope and has a broader perspective than the Team's paper on the Agency's BA/BE questions. There are some significant areas of overlap between the Team's two papers and therefore we request that the Agency and OINDP Subcommittee consult both papers for a complete perspective of the Team's consensus views on BA/BE issues.

The Team has prepared this paper on in vitro and in vivo tests in the draft BA/BE Guidance in order to:

- highlight areas where there are not enough data at present to draw conclusions; and
- review available technical documentation related to BA/BE issues addressed by the Team and offer the Team's conclusions based on that documentation.

The conclusions of this paper are applicable to the draft BA/BE Guidance for Nasal Aerosols and Nasal Sprays for Local Action as well as the Agency's forthcoming draft BA/BE Guidance for orally inhaled drug products. It is recognized that this paper contains relatively few examples relating to nasal issues because of the lack of pertinent nasal data available. Although most of the examples are for pulmonary locally acting drugs, these data may have general applicability to nasal drugs and will be directly relevant for the Agency's future guidance on orally inhaled drug products.

IV. ASSUMPTIONS AND OTHER CONSIDERATIONS

1. Assumptions of BA/BE Technical Team

In preparing this paper, the BA/BE Technical Team has agreed on the following working assumptions:

- Our specific BA/BE recommendations apply to locally acting drugs per the current draft BA/BE Guidance for nasal aerosols and sprays, and should apply, as appropriate, to orally inhaled drug products in the anticipated forthcoming BA/BE Guidance for orally inhaled drugs;
- Our conclusions apply to both orally inhaled and nasal drug products, but these dosage forms should be treated in separate Guidances;
- Scientific and clinical bases for developing BA/BE Guidance are evolving; and
- Our BA/BE working propositions reflect only the current state of knowledge.

2. Definition of Bioequivalence (BE)

As noted in the draft BA/BE Guidance, BA and BE may be established in vivo by measuring both local delivery and systemic absorption/exposure. The draft Guidance equates local delivery with efficacy studies and systemic absorption/exposure with pharmacokinetic (PK) or pharmacodynamic (PD) studies. The BA/BE Team has discussed situations where use of in vitro data plus systemic PK/PD studies may be sufficient to establish BE. This discussion can be found in the BA/BE Team's companion paper which has been submitted to the Agency with this paper.

3. Factors Relating In Vitro Tests to Deposition and to Biological Effect

The biological effect of an inhaled drug is dependent on several factors. First is the mass of particles in the inhaled air stream (emitted dose). Particle size distribution, breathing pattern, and the specific nature of the aerosol delivery from the device are the prime determinants of the deposition pattern in the body. Other deposition factors include the geometry of the airways that can be influenced by disease state. The drug may act locally in the region of deposition, or at a remote site following absorption of the drug into the blood stream and systemic delivery. Thus, there are many factors that can influence biological effect other than the particle size distribution and emitted dose of the inhaled drug, as has been noted in several reviews (Schlesinger, 1988; Gonda, 1990; Brain and Blanchard, 1993).

The use of in vitro tests of particle size distribution and emitted dose as surrogates for deposition or biological effect must be approached with caution as has been noted previously by individuals and groups assessing this issue. There have been at least two workshops that have examined this question in some detail (Clark, 1998; Snell and Ganderton, 1999). The consensus from both meetings was that in vitro / in vivo comparisons are being developed and in vitro methods are improving to enhance their in vivo applicability, but that as yet it is not possible to rely solely on in vitro data as a predictor of clinical use by patients. The proceedings from these workshops provide in depth considerations of various aspects of this general question and are excellent sources for more detailed discussions.

V. TEAM'S POSITION STATEMENTS

The Team's position statements on in vitro and in vivo tests in the draft BA/BE Guidance are as follows:

1. In Vitro Tests:

In vitro testing is essential for pharmaceutical product equivalence and should be included as part of BA/BE Guidance for all nasal and oral inhalation products, but is not currently sufficient for BE approval without establishing in vivo BE.

2. In Vivo Tests*:*

For BE approval, BA/BE Guidance documents for nasal and oral inhalation drug products for local action should require use of validated human models for in vivo testing for local and systemic exposure, efficacy and safety.[2]

[2] As addressed in more detail in the BA/BE Team's paper responding to the FDA's BA/BE questions, it is appropriate that sponsors be given the opportunity to present their case for an abbreviated clinical program. If a predictive in vitro/in vivo correlation can be documented from the literature or from new well-documented data, the sponsor should have the opportunity to request waiving all clinical studies.

VI. In Vitro Tests in Draft BA/BE Guidance

1. Overview of In Vitro Tests in Draft BA/BE Guidance

The draft BA/BE Guidance utilizes a large battery of in vitro tests in order to evaluate drug product quality of nasal and inhaled dosage forms. In particular, the following tests have been identified in the draft BA/BE Guidance as part of BA and BE determination:

1. Dose or Spray Content Uniformity
2. Droplet and Particle Size Distribution
3. Spray Pattern
4. Plume Geometry
5. Priming and Repriming
6. Tail Off Profile

Spray content uniformity, particle size distribution, spray pattern and priming (if part of product labeling) are considered in vitro determinants of BE utilizing the confidence interval approach. Plume geometry, tail off profile, and particle size characterization through light microscopy may be evaluated as supportive characterization of BE. The draft BA/BE Guidance stresses the importance of conducting in vitro testing in a randomized, blinded fashion in order to eliminate potential analyst bias.

In the following sections, we highlight the issues which have been raised surrounding the use of these tests for the investigation of BE alone or in combination with an in vivo assessment.

2. BA/BE Team's Analysis

2A. In vitro tests described in the draft BA/BE Guidance are not necessarily more relevant or discriminating than clinical studies for BE assessment

The establishment of BA and BE in nasal products for local action requires reliance on clinical endpoint studies. The draft BA/BE Guidance acknowledges that studies of this nature are frequently incapable of showing a dose-response relationship and may not be consistently reproducible. However, in vitro tests for demonstration of bioequivalence also have limitations.

Of the tests utilized for in vitro assessment of nasal and inhalation drug products, droplet and particle size data have received the most attention in the literature. According to the draft BA/BE Guidance, droplet and particle size distribution can be evaluated through several methods, including optical methods (laser diffraction, light scattering, time-of-flight), inertial impactor methods (cascade impactor, multistage liquid impinger), and light microscopy.

Laser diffraction is the suggested method for determination of droplet size distribution. It is especially useful for nasal sprays, because it has enough size range to cover large nasal droplets produced by nasal sprays (Cheng *et al.*, 2000). In general, the method is fast, has good resolution, a broad particle size range, and can be used for measurements of pMDIs, DPIs, and liquid atomizers such as nebulizer systems. The great disadvantage of laser diffraction methods is that they cannot differentiate components of the formulation. In the case of pMDI systems, other disadvantages include sampling errors due to evaporation, overestimation of size distribution due to presence of propellant s, and dilution requirements (Dolovich, 1991; Clark *et al.*, 1998).

Another optical method currently receiving attention is the time-of-flight aerodynamic particle size analyzer. Similar to laser diffraction techniques, this method cannot discriminate between drug and non-drug particles. This method has been investigated for use with pMDIs, DPIs and nebulizers. The present state of the art suggests that this particle sizing method is effective for formulation development and screening, but cannot replace inertial particle size methods such as those described in pharmacopoeial compendia (Mitchell *et al.*, 1999).

Inertial particle size techniques, such as cascade impactors and multistage liquid impingers have a distinct advantage since the methods are capable of distinguishing drug particles, normally through an assay technique. However, the limitations of this method have been well documented. Size distributions among cascade impactors can vary significantly, and thus any comparisons performed in order to establish BA or BE must be evaluated with the same equipment (Stein and Olson, 1997; Stein 1999). In addition, there is concern regarding the use of this equipment for evaluation of nasal products, given that particle sizing stages have been optimized for oral inhalation products, and not for nasal delivery, where MMAD exceed 10 μm (Harrison, 2000).

The spray pattern/plume geometry including plume angle and speed of the plume are also important factors on the distribution of deposited droplets in the nasal airway, and may therefore influence the bioequivalence of nasal drugs (Cheng *et al.*, 2000). High speed photography/video is used to determine the plume geometry/spray pattern. Therefore, we suggest that light microscopy be strictly used as a supportive method for drug and aggregate particle size and morphology evaluation, because of its limitations.

We also believe that in vitro tests are important for the establishment of BA and BE, particularly dose content uniformity and particle size analysis. However, the predictive limitations of the in vitro tests at the present time support the need for in vivo studies.

2B. The assumption that in vitro studies alone are sufficient for BE of solutions is unfounded. The draft BA/BE Guidance should not distinguish between nasal suspensions and solutions for in vivo BE

According to the draft BA/BE Guidance, in vitro tests are sufficient to support approval of solution nasal products. As documented in this paper, in vitro tests for use as BE metrics have limitations. Based on the lack of information on the established relationship between in vitro/in vivo data for OINDP, it is the consensus of the BA/BE Technical Team that in vivo BE determinations should be required. As more data becomes available, removal of in vivo BE testing for solutions could be considered for certain drug classes.

2C. Based on the available literature, current in vitro tests may predict lung deposition, but the utility of those tests to demonstrate clinical equivalence of inhaled drug products has not been shown

The clinical relevance of in vitro data to the in vivo environment has been studied for a variety of products, including inhalation dosage forms. In particular, in vivo lung deposition has been demonstrated to be linked to in vitro estimates of fine particle dose in well controlled studies for cromolyn sodium (Laube *et al*., 1998). However, such correlations may not hold true for all cases and classes of drug substances used in inhalation and nasal dosage forms. In addition, the ability of in vitro studies to predict clinical effectiveness in general has not been demonstrated. This is an evolving area with considerable promise, but there is yet no validated approach of wide-ranging applicability.

A review of the literature indicates that in certain instances, in vitro results have failed or inaccurately predicted the in vivo results, which would have resulted in a false conclusion regarding BE if in vivo studies had not been conducted. Failure to predict in vivo outcome has been demonstrated in the following two studies. In a study by Borgström *et al.* (2000), the in vitro and in vivo performance (lung deposition) of terbutaline via a pMDI and DPI Turbohaler was evaluated. The variability in lung deposition could not be attributed solely to in vitro variability, which is linked mainly to variability in dose leaving the metering chamber/dosing disk. The interaction of patient geometry (anatomy) and the actual patient handling of the device had a significant influence on the overall variability, which could not be mimicked in the in vitro environment. In another study, two nasal aerosols with different in vitro properties were generated. Although in vitro testing concluded significant differences among the two aerosols, this did not translate into any differences in the in vivo deposition pattern in the nose (Suman *et al.*, 1999). Similar nasal deposition patterns with differing particle sizes was also observed by Hughes *et al.* (1993). The lack of difference in deposition pattern could be a result of poor power of discrimination in the in vivo test and emphasizes the difficulty of measuring nasal deposition patterns in vivo.

Inaccurate predictions of in vivo deposition have also been demonstrated in several studies. A comparison of 11 scintigraphic studies and fine particle fraction measurements conducted on MDIs, DPIs and Soft Mist Inhalers found that in vitro assessment provided an overestimation of actual lung deposition (Newman, 1998) when the standard cut-off diameter of 4.7 micrometers was used. However, Newman (1998) showed that there was a much improved correlation of lung deposition with particles less than 3.3 micrometers. However, it should be noted that this correlation is in all probability descriptive, not predictive; different correlations may be obtained if there are variations in the method used to assess deposition. Another study conducted by Olsson *et al.* (1996) demonstrated improvement in correlation between lung deposition and fine particle fraction through modification of the inlet port on the impinger to mimic the oropharynx. Other recommendations to improve correlations between in vitro measurements and in vivo deposition include use of a multistage apparatus in the range of 0.5 – 5.0 µm. and evaluation on a range of flow rates to mimic the in vivo conditions (Snell and Ganderton, 1999). A recent study on the AERx inhalation system indicated good correlation between the in vitro measurement and in vivo deposition pattern when similar flow rates were utilized (Farr *et al.*, 2000).

The current literature suggests that we can use the available knowledge on the relationship between in vitro and in vivo outcome to run in vitro studies during biopharmaceutical development, but we cannot at the present time use in vitro methods alone to claim in vivo / clinical effect equivalence as a basis for regulatory approval.

VII. IN VIVO TESTS IN DRAFT BA/BE GUIDANCE

1. Overview of In Vivo Tests in Draft BA/BE Guidance

The BE tests[3] recommended by the BA/BE Team for all nasal and orally inhaled drugs fall into the following scheme:

- Clinical efficacy study to document equivalent drug delivery to the local site of action; and
- Systemic exposure study (PK).

The clinical efficacy study is used to assess local delivery of drug and efficacy, whereas the systemic exposures are intended to provide a marker that can be related to safety. Some of the challenges involved in conducting meaningful in vivo studies are that some endpoints are easier to measure than others for particular classes of drugs. This means that it is frequently difficult to assess both local and systemic criteria adequately for all drugs.

For instance, for nasal drugs, it is difficult to have clinical responses that can differentiate two products. However, it may be more difficult to measure systemic exposure of the nasal products considering the low doses administered. For orally inhaled bronchodilators, good methods of quantifying bronchodilator response have been identified (Adams, 1995; Stewart *et al.*, 1999). It is, however, relatively difficult to ascertain a dose-response relation related to efficacy for orally inhaled corticosteroids. These difficulties in adequately assessing BE have been cited frequently (Adams *et al.*, 1994, 1995, 1998; Wong and Hargreave, 1993, Casale *et al.*, 1999; Harrison, 2000). These complexities and differences between exposure routes, classes of drugs, and specific drugs, argue for more flexible approaches. Although the BA/BE Team agrees that the above in vivo BE program should be recommended in the draft BA/BE Guidance, the Team also recommends that the BA/BE Guidance urge sponsors to discuss their in vivo BE program for a specific drug with the Agency.

The following specific issues identified by the BA/BE Technical Team emphasize that both clinical efficacy and systemic exposure (as an indicator of adverse effects) need to be evaluated to provide an adequate assessment of clinical BE.

2. BA/BE Team's Analysis

2A. Systemic PK/PD estimates systemic exposure (*i.e.*, safety) but does not estimate local delivery (*i.e.*, efficacy and local tolerance).

Blood levels of a particular drug obviously reflect the amount of drug absorbed systemically. However, for respiratory tract drugs, absorption can take place from the site of absorption, across tissue and into blood, and also from drug that is translocated by mucociliary clearance from nasal or bronchial airway epithelium, swallowed and then absorbed from the

[3] In this paper, BE is assumed to be BE of clinical efficacy and safety.

gut. Further, there can be differential rates of absorption from various sites in the lung. Many data sets show a higher degree of absorption from the alveolar or pulmonary region than from upper airways (Oberdorster, 1986) although this is compound dependent and is more evident for larger than smaller molecules. Available data support the view that local topical delivery of corticosteroids is responsible for their clinical efficacy both with nasal delivery (Howland, 1996a, 1996b; Lindqvist *et al.*, 1989) and for orally inhaled delivery (Toogood *et al.*, 1990; Lawrence *et al.*, 1997). As a corollary, because the same systemic blood levels can be achieved by different deposition patterns, systemic exposure does not necessarily correlate with efficacy. Thus, we concur with the Agency's position as stated in the draft Guidance.

2B. Efficacy assessments alone cannot establish in vivo BE since they will not assure comparable safety (systemic exposure)

Local delivery BE studies are important to assure equivalent efficacy and local tolerance at the site of action, but the study design does not assure systemic safety, which is a major concern of a new product. Literature data clearly indicates that systemic absorption (as measured by PK) may not correlate with local delivery. Studies comparing oral administration with either nasal or oral inhalation administration for fluticasone propionate and budesonide (see references in the previous section) have shown no correlation between PK and clinical efficacy. Until a linkage is established for a given drug or drug class, caution is advised against any modification of the proposed in vivo BE program that includes both local delivery and systemic absorption/exposure. Thus, we concur with the Agency's position as stated in the draft Guidance.

2C. Lung deposition studies are a promising new technique, but currently cannot replace the local delivery requirement

Local delivery estimated as total material deposited in the lung is not likely to be sufficiently discriminating to be predictive of BE. Two examples are examined to illustrate this point. In a study by Leach (1998), HFA and CFC formulations of beclomethasone dipropionate were compared. Although the emitted doses were the same, the fine particle dose (percent of particle mass < 4.7 micrometers) was higher for the HFA formulation compared to the CFC formulation (56% of emitted dose vs 33%,respectively). Deposition was dramatically different, with the HFA formulation (1.1 μm MMAD) resulting in 56% lung deposition vs 6% for the CFC formulation (3.9 μm MMAD). Clinical efficacy studies showed that the HFA beclomethasone dipropionate formulations did not scale directly with lung deposition, but required approximately half the emitted dose of the CFC formulations. In a non-clinical example, Ruffin *et al.* (1978) compared bronchoconstrictive effects of histamine when inhaled in different modes. Equal lung doses of histamine were given in one mode with a central deposition pattern and in the other mode with a peripheral deposition pattern. Although the total lung doses were equal, the bronchoconstricting effect of histamine was much greater for the central deposition pattern.

The Leach and Ruffin papers point out that regional deposition pattern within the lung is very important for eliciting a biological response, which can differ even if the total lung dose is the same. For instance, bronchodilator response to beta-2 agonists appears to be predominantly related to receptor mediated action on bronchial airway smooth muscle (Barnes, 1995; Nishikawa *et al.,* 1996). Therefore if two formulations have the same total lung dose but differing bronchial airway doses, biological response is likely to differ. Other drugs with different receptor distributions in the lung and other modes of action will have to be considered on an individual compound basis. If this is the case, then knowing total lung dose will not be sufficient to determine biological response for all pharmacologic agents.

A limitation of the most common lung deposition technique is that the product must be altered by the sponsor to allow for the addition of a radiolabeled tag. In order for the radiolabeled material to serve as a BE standard, data must be provided to show that product properties are essentially unchanged and remain within specifications. Another limitation of the radiolabeled lung deposition technique is that at present, there is no standardized approach to such a study.

2D. Reduction of testing requirements with validated models

In vitro data, regional deposition data, PK/PD studies, and clinical efficacy studies are all likely needed to characterize adequately the relationships going from inhaler and particle characteristics to relate to ultimate clinical effects in patients when a new inhaled drug is developed (Borgström, 1999; Gonda, 1990). (The data derived above for the new HFA formulation of beclomethasone dipropionate is a good example). With sufficient data it should be possible to define the variations around the individual components that results in clinically similar efficacy. Various linkages among the data sets can be envisaged.

If it is possible to determine that a certain range of regional deposition values or PK parameters or in vitro test results correlates with in clinical efficacy within acceptable limits, then future studies might need only to measure regional deposition or PK or in vitro testing within these ranges. Further, if these features could be reliably linked with mathematical models that predict a range of deposition behavior or PK performance or in vitro test results for given input parameters it would be possible to reduce or eliminate reliance on carrying out extensive clinical trials. Until the state of the art improves such that there is more power among the tests relating in-vitro tests to ultimately predict clinical effects, it appears a cautious approach is warranted (Wong and Hargreave, 1993). It is impossible at this time to completely describe a validated model because it will depend on the available data for the particular inhaled drug being developed, and so it is recommended that an approach for each circumstance be negotiated between the sponsor and regulatory agencies.

VIII. CONCLUSION

The ITFG and IPAC share the FDA's goal of assuring the highest levels of safety, efficacy and quality of orally inhaled and nasal drug products and making these products available to patients in the most expeditious manner. We recognize and appreciate the considerable efforts put forth by the Agency in developing guidance on product quality BA and BE studies for OINDP. The ITFG/IPAC Collaboration also commends the Agency for addressing key issues in BA and BE studies at the 26 April OINDP Subcommittee meeting. We are grateful for the opportunity to share with the Agency and the OINDP Subcommittee our perspectives on in vivo and in vitro studies in the draft BA/BE Guidance.

Our comments in this paper are intended to highlight areas in the draft BA/BE Guidance where the scientific rationale can be questioned and where more scientific discussion and debate are needed. The Agency's comments to the OINDP Subcommittee on 26 April underscore the Agency's concerns with some of the positions in the draft BA/BE Guidance. We encourage the Agency to solicit further scientific discussion on these positions before issuing further guidance. In addition, the members of the ITFG/IPAC Collaboration strongly recommend that the Agency continue to utilize existing avenues for scientific collaboration, such as the OINDP Subcommittee of the Advisory Committee for Pharmaceutical Science, the Product Quality Research Institute (PQRI), or another AAPS/FDA/USP workshop on Regulatory Issues Relating to Drug Products for Oral Inhalation and Nasal Delivery to gather all interested parties for a data-driven scientific review of key BA/BE issues.

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